P. ginseng in Reactive Oxygen Species-Mediated Diseases

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Reactive oxygen species (ROS)-the byproduct of regular cell activity formed by various cellular components—play a significant role in pathological and physiological conditions. Alternatively, antioxidants are compounds that reduce or scavenge reactive species in cells. An asymmetry between the antioxidant defense system and ROS from intracellular and extracellular sources cause chronic diseases such as cancer, inflammation, tumorigenesis, cardiovascular and neurogenerative diseases. *P. ginseng* and its derivatives are some of the antioxidant-rich sources involved in the regulation of many oxidative-stress-related pathways.

Keywords: ROS ; antioxidant ; oxidative stress ; Panax ginseng

1. Introduction

Ginseng comes from the genus *Panax* of the *Araliaceae* family with nine different species such as *Panax ginseng* (Korean ginseng), *Panax notoginseng* (Chinese ginseng), *Panax japonicum* (Japanese ginseng), and *Panax quinquefolius* (American ginseng) [1]. Among all ginseng, four types of *P. ginseng* can be categorized according to how they are processed, for example, fresh ginseng, white ginseng (air-dried), red ginseng (steamed), and sun ginseng [2]. The word “ginseng” is derived from the Chinese word “rénshēn” which means “human” as the roots of ginseng are shaped like the human leg [3]. Ginseng has long been recognized as ‘the king of herbs’ due to its ability to improve fitness and relax the mind [4]. *P. ginseng* is endemic to Korea and China and has been used in traditional treatment [5]. However, consumers from Korea and others prefer Korean ginseng due to its current medical research findings of being useful in boosting blood circulation and better cognition, acting as a mind booster, and it being supposed to bolster one’s soul, increase the body’s immune system, and control diabetes, along with possessing anti-aging and anticancer properties [6][7]. *P. ginseng* contains a vast amount of secondary metabolites such as phenolic acids (gallic acid, caffeic acid, coumaric acid, salicylic acid, cinnamic acid, maltol, etc.), flavonoids, acid polysaccharides, amino acids, phytosterol, carbohydrates, minerals, ginseng oil, and certain vitamins [4][8]. *P. ginseng* has attracted the interest of researchers worldwide due to its pharmacological efficacy and potent medical applications.

Instead of entire ginseng and other components, a majority of researches have been conducted on specific ginsenosides to treat a variety of medical problems [9]. Ginsenosides are mainly triterpene saponins of ginseng. To date, more than 218 ginsenosides (major types: Rc, Rb1, Rb2, Rg1, Rd, and Re; minor types: Rh1, Rh2, and Rg3) have been identified from different parts of ginseng (leaves, roots, berries, and flower buds) and these metabolites have become popular for research. Ginsenosides are the therapeutically active components obtained from ginseng and are widely recognized for their oxidative stress [10], apoptosis [11], inflammation [12], angiogenesis [13], anticancer [14], and cancer metastatic properties associated with cell proliferation. Ginsenosides are divided into two groups based on the glycon structure: oleanane and dammarane [15]. According to the chemical structure, dammarane-type ginsenosides can be further classified into two categories: protopanaxadiol (PPD) and protopanaxatriol (PPT) [16], whereas the minor categories depending on aglycone moieties include ocotillol and oleanane [17]. Ginsenosides Rc, Rb2, Rh2, Rg3, Rh4, Ck, Rk1, Rk3, and Rd are strong bioactive components that have been shown to greatly inhibit the proliferation of cancer cells by regulating ROS in mitochondria [18]. The following are listed in decreasing order of how well ginsenosides scavenge intracellular ROS: Rb2 > Rc > Rg2 > Rh2 > Rh1 > Rf > Rg3 > Rg1 > Rb1 > Re > Rd [19]. Different studies have shown that the transformation of ginseng referred to as ginsenosides have stronger activity than crude ginseng [20].

P. ginseng and ginsenosides have excellent ROS-regulating activity in various disease families such as sensor impairment, cardiovascular diseases, neurogenerative diseases, cancer, diabetes, inflammation, and vice-versa.

2. ROS, Oxidative Stress, and Antioxidants

Reactive oxygen species (ROS) including hydrogen peroxide (H_2O_2), superoxide ($O_2\cdot$), and hydroxyl ($HO\cdot$) radicals were initially recognized as potentially hazardous by-products; they are now acknowledged to serve significant roles as secondary messengers in numerous intercellular pathways [21]. ROS are produced during ATP production by the electron transport chain and NADPH (nicotinamide adenine dinucleotide phosphate) oxidase system [22]. Moreover, our bodies usually produce huge amounts of ROS due to our daily lifestyles including extended working circumstances, sitting for a long time, wearing restrictive clothing, using illicit substances often, eating unhealthily, and smoking or drinking too much alcohol [23]. ROS positively impact on immunological activity and intracellular signaling at mild to moderate levels [24]. A higher concentration of ROS can cause oxidative stress, DNA damage, redox homeostasis, tumor progression, and drug resistance which are related to the development of various diseases. ROS play a crucial role in cell proliferation, differentiation, and the control of signal transduction at certain levels (**Figure 1**) [22]. According to Sies (1985), "Oxidative stress is defined as the imbalance of pro-oxidant and the antioxidant protective capacity that promotes ROS or RNS which might cause potential damage" [25]. Undeniably, oxidative stress is associated with more than 100 diseases as a source or outcome [26][27]. It is well known that oxidative stress leads to cell death by damaging important bio-compounds such as proteins, DNA, and lipids [28]. Oxidative stress acts as a contributor to many chronic diseases such as cancer, neuro-generative disease, inflammation, cardiovascular disease, etc. [29].

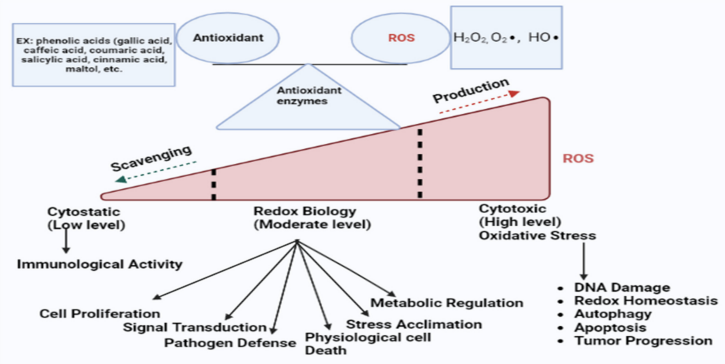

Figure 1. In normal cells, the balance between antioxidants and ROS remain at equilibrium due to the chemical reactions of antioxidant enzymes (SOD, CAT, GPx, and GST). However, the overproduction or scavenging of ROS breaks this equilibrium system. At the moderate or basal state, ROS perform as secondary messengers in several intracellular pathways that are essential for healthy cells. However, higher concentrations of ROS can cause oxidative stress, DNA damage, redox homeostasis, autophagy, apoptosis, tumor progression, and drug resistance which are related to the development of various diseases.

On the other hand, an antioxidant is a compound that reduces or scavenges reactive species or blocks the oxidation in cells [30]. In other words, antioxidants have the power to stop or delay the oxidation reaction to regulate the excessive production of oxidants [31]. Thiols and polyphenols are common examples of antioxidants for their reducing behavior [32]. Plants and animals consist of two types of antioxidants: non-enzymatic (vitamin E, C, carotenoids, lipoic acid, and others) and enzymatic (catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), Glutathione-S-Transferase (GST), Glutathione reductase (GR), etc.). These enzymatic antioxidants have important functions in regulating cell homeostasis [33]. In a nutshell, the antioxidant mechanisms are (a) inhibiting the production of reactive species, (b) scavenging oxidants, (c) restoring the damaged molecule, (d) blocking the formation of harmful secondary metabolites and inflammation mediators, and (e) developing and boosting the natural antioxidant defense system. These defensive mechanisms work together to prevent oxidative stress in the body [34]. However, in redox biology, superoxide dismutase quickly turns into H_2O_2 and O_2 via the SOD enzyme. The Fenton reaction can decrease metal ions to produce $OH\cdot$ from H_2O_2, which is issued in systemic inflammation [35][36]. $OH\cdot$ are reactive and so damages macromolecules. Antioxidant enzymes (catalase, glutathione peroxidase) can detoxify H_2O_2 to avoid the production of $OH\cdot$ (**Figure 2**).

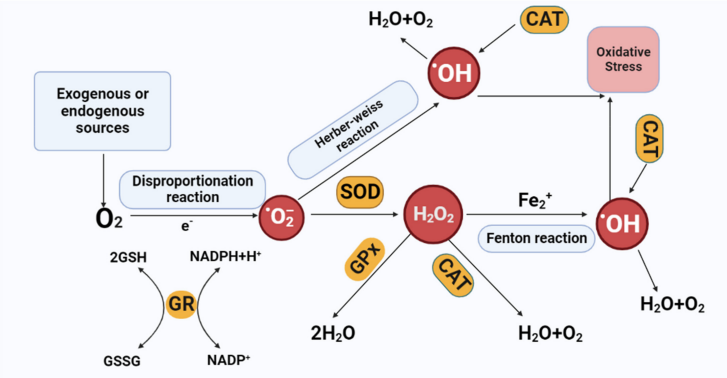

Figure 2. Scavenge and production of reactive oxygen species (ROS). Organic and inorganic constituents can produce, convert, and scavenge ROS. Antioxidant enzymes (SOD, CAT, GPx, and GR) intercept ROS through the chemical reactions. Oxidases convert oxygen to $O_2^{\cdot-}$, which is then dismutated to H_2O_2 via SOD. H_2O_2 can be converted to H_2O via CAT or GPx or to hydroxyl radical (·OH) after reaction with Fe^{2+}. **Abbreviations:** SOD-Superoxide dismutase, CAT-catalase, GPx-glutathione Peroxidase, GR-glutathione reductase. GSH-glutathione. GSSG-glutathione disulfide. $O_2^{\bullet-}$-superoxide anion. H_2O_2-hydrogen peroxide, (HO·)-hydroxyl, ROS-reactive oxygen species.

Natural antioxidants have numerous biological effects including preventing ROS production and inhibiting free radicals [37]. The administration of natural sources of an antioxidant such as ginseng, pomegranate, curcumin, sesame, garlic, peppermint, and olive leaves demonstrated beneficial effects on ROS-mediated diseases in both animal and human studies [38][39].

3. *P. ginseng* in ROS-Mediated Diseases

In mammalian cells, mitochondria are significant for pathophysiological processes including oxidative phosphorylation (OXPHOS), the formation of cell development, and mediating key events that determine cell functions and states. According to some reviews, many diseases such as I/R injury, cardiovascular diseases, neurogenerative diseases, cancer, and metabolic disorders have been linked to mitochondrial dysfunction [40]. Several studies have demonstrated that *P. ginseng* regulates mitochondrial ROS, apoptosis, dynamics, biogenesis, and mitophagy to have a pharmaceutical impact. The overexpression of mitochondrial ROS leads to a wide variety of disorders and many of them lead to causes of death [41] which have been summarized below.

3.1. Antioxidant Activities of P. ginseng in Sensor Impairment

3.1.1. Ototoxicity

Age-related hearing loss is considered to be an ROS-mediated disorder. Other causes of hearing loss are noise, antibiotics (Aminoglycoside, cisplatin) consumption, and immune-mediated hearing loss [42]. Many studies have exhibited that ginseng is helpful to prevent ototoxicity caused by different sources. Aminoglycosides including gentamicin react with iron in the inner ear and produce ROS with damage to hair cells and neurons. Choung et al. showed that ginsenoside Rb1 and Rb2 are effective against aminoglycoside-induced hearing loss by attenuating ROS generation and IL-6 inhibition [43]. The organ of Corti reaches its maximum intensities of ROS and RNS generation after seven to ten days of noise insult [44]. Additionally, ginsenoside Ck and Rg2 have therapeutic effects against noise-induced hearing loss in mice by reducing the levels of ROS and RNS [45]. Ginseng extract protects against cisplatin-induced ototoxicity of the auditory cell line (HEI-OC1) due to its anti-apoptotic and anti-oxidative stress effects [46].

3.1.2. Ocular Disease

It is believed that oxidative stress is involved in many age-related eye illnesses including retinal degeneration and cataract, glaucoma, and diabetes retinopathy, etc.; cataract is an age-related loss of transparency of the eye lens because of the formation of protein complexes in the lens [47][48][49]. ROS and ultraviolet radiations damage crystalline proteins during aging, resulting in the insoluble protein clumps of the lens being opaque which interferes with vision. Park et al. recognized that ginsenoside CK blocked ROS production via Nrf2/HO-1 activation in the H_2O_2-stimulated ARPE-19 cell line to prevent cataracts [49]. After cataracts, glaucoma is the second leading reason for blindness which is associated with intra-ocular pressure and a loss of vision [50]. An overproduction of ROS leads to apoptosis in retinal ganglion cells that cause glaucoma [51]. Several studies showed evidence that ginseng supplements and ginsenosides are very useful against glaucoma. Ginsenoside Rb1 protects retinal ganglion cells against apoptosis caused by H_2O_2-induced oxidative stress [52]. Moreover, patients with glaucoma who consumed 3 g of Korean red ginseng daily for 4 weeks observed an

improvement in their daytime visual acuity and ocular pain [53]. Eight weeks of consumption of KRG reduces the symptoms of dry eye in glaucoma patients by improving the tear film stability [54].

3.2. Antioxidant Activities of P. ginseng in Neurogenerative Diseases

The central nervous system (CNS) is extremely vulnerable to oxidative injury due to its utilization of a high pace of oxygen [55]. An overproduction of ROS and inadequate antioxidant defense systems have been connected to the pathophysiology of numerous neurogenerative disorders such as Huntington's disease (HD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Alzheimer's disease (AD) [56]. Neuroprotection inhibits or delays the neurogenerative process to minimize neuronal death [57]. In this case, secondary metabolites of plants which are rich in antioxidant content can protect the nerve cells from free-radical-induced oxidative stress to prevent neurogenerative diseases [58]. The research into and recognition of the potential impact of *Panax ginseng* on ROS-mediated neurogenerative diseases are growing day by day.

3.2.1. Parkinson's Disease

Parkinson's disease (PD) is a chronic neurodegenerative condition that affects approximately 2% of people over 60 years old worldwide. PD depends on the interplay between various genetic and environmental factors and is marked by the development and accumulation of misfolded-α-synuclein [57]. The hallmark symptoms of PD include motor disorders (rigidity, tremor, and bradykinesia) and non-motor disorders (depression, sleep disturbance, and autonomic dysfunction) resulting from the gradual deterioration of the dopaminergic pathway [59]. Several studies have depicted that ginseng and its bioactive components, ginsenosides, have therapeutic actions on PD. *P. ginseng* extracts can inhibit ROS generation, eliminate Bax/Bcl2, increase the cytochrome C release, and stimulate caspase-3 expression to alleviate cell death [60]. Ginsenoside Rg1 suppressed the oxidative stress to mediate the neuroprotective action in MPTP (1-methyl-4-phenyl-1,2,3,6-twtrahydropyridine)-induced substantia nigra [61][62]. Rg1 activates total superoxide dismutase (SOD) and inhibits glutathione reduction, reducing c-Jun and N-terminal kinase (JNK) in the substantia nigra of C57BL/6 mice [61]. Furthermore, Rg1 decreases ROS production and mitochondrial cytochrome C and blocks the activation of caspase 3 and the formulation of the iNOS protein and NO in PC12 cells [63]. Again, Rg1 attenuates ROS generation and NF-κB translocation in MPP+-induced MES23.5 cells for reducing the expression of DMT1-IRE [64]. Ginsenoside Re shows neuroprotective action against the neurotoxicity of substantia nigra. Ginsenoside Re increases the Bcl-2 mRNA and Bcl-2 protein expression decreases the iNOS, Bax, and Bax mRNA and inhibits the cleavage of caspase-3 to protect the SN neuron from MPTP-induced apoptosis [65].

3.2.2. Alzheimer's Disease

Alzheimer's disease (AD) is a cognitive condition defined by the accumulation of senile plaques, the development of neurofibrillary tangle, and finally the death of neurons. The improper degradation of the amyloid precursor protein (APP) is the primary mechanism causing AD progression [66][67]. Several changes in molecular and cellular pathways including mitochondrial dysfunction, antioxidant decreases, oxidative stress increases, synaptic impairment, and amyloid Aβ clearance capacity are present in the AD brain [68][69][70]. Many studies have distinguished that *P. ginseng* extract, powder, and ginsenosides were applied to AD in in vivo and in vitro studies. The total saponins of ginseng consumption for seven months revealed a remarkable reduction in memory loss by inhibiting oxidative stress and increasing the proteins associated with plasticity in aged mice [71]. Ginsenoside Rb1 shields neurons from Aβ1-42 neurotoxicity via an antioxidant mechanism [72]. Rb1 pre-treatment in PC12 cells for 1 day inhibits the overproduction of ROS and lipid peroxidation enhances the activation of caspase-3 and Bcl-2/bax for promoting cell survival [73]. In H_2O_2-induced PC12 cells, Rg1 prevents NF-κB/P65, ERK1/2, and Akt stimulation [74]. Rg1 can protect PC12 cells from cytotoxicity caused by Aβ25-35 by preventing β-secretase activities [75]. However, the ref. [76] experiment found for the first time that ginsenoside Rk3 can trigger the intracellular ROS level and Aβ-induced neuronal injury by stimulating the AMPK pathway and the upregulation of Nrf2. Interestingly, this research also confirmed that the pharmacological activity of ginsenoside Rk3 is better than the control drug donepezil in case of the treatment of AD. Recently, a new ginseng component gintonin has been discovered that is effective in reducing the severity of AD-related neuropathies [77].

3.2.3. Others

P. ginseng and its active components are also effective in Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), depression, neuroprotection, and improvement in cognition [78]. Wang et al. recognized that ginseng sesquiterpenoids down-regulate the NF-κB and BDNF/TrkB signaling pathways, and increase SOD production in the hippocampus of the ICR mice model. The result exhibited that the SP of ginseng shows antidepressant activity via Sirt1/NF-κB and BDNF/TrkB pathways [79]. Water extract of Korean red ginseng acts as a neuroprotector through the regulation of the Nrf2 signaling pathway [80]. Ginsenoside Rb1 exhibits strong antioxidant activity in the treatment of many neurological diseases

including strokes [81]. Ginsenosides Rg3 and Rg1 are useful in cognition improvement via regulating the NF-κB and PI3K/Akt signaling pathways in mice models [82][83]. It has been reported that *P. ginseng* fibrous root (GFR) shows good antioxidant activity to scavenge free radicals. GFR enhanced the expression of antioxidant enzymes to trigger the intracellular ROS which ultimately accelerated Alzheimer's and other neurogenerative diseases [84].

3.3. Antioxidant Activities of P. ginseng in Cardiovascular Diseases

Cardiovascular disease (CVD) is a critical challenge among 50% of the world's population [85]. CVD includes hypertension, coronary artery disease, massive heart failure, and peripheral vascular disease, etc., which are common and affect newborns, children, and adults of both sexes [86]. Research shows that the enhancement of reactive oxygen species and oxygen consumption is one of the crucial factors in CVD outbreak. For example, heart failure can be caused by ROS-inducing cardiac apoptosis and necrosis [87][88], as well as increased oxidant generation via the NADH/NADPH oxidant, and superoxide-generated endothelium breakdown results in hypertension and coronary artery disease [89][90]; furthermore, an overproduction of ROS and oxidant-mediated myocyte apoptosis and necrosis causes myocardial infarction [91][92]. An excessive amount of free oxygen from heart ischemia causes myocardial damage; however, ginseng consumption increases blood flow by inhibiting free oxygen and myocardial damage [93]. Ginsenoside Rb1 can inhibit the production of ROS to reduce homocysteine which causes endothelial dysfunction [94]. Ginsenoside Re protects the myocardial cell from oxidative damage and increases myocardial cell viability in heart ischemia [95]. Total ginsenosides enhance coronary artery perfusion flow by activating the PI3K/Akt-eNOS signaling pathway that ultimately produces NO levels [96]. Ginsenoside-Rb1 administration increases eNOS expression which also increases NO levels and decreases super oxides in the porcine coronary artery via the vasodilating mechanism [94]. In addition, the saponin fractions of Korean red ginseng decrease blood pressure and prompt reflex tachycardia due to their hypotensive effect and the mechanism of NO donation [97]. In another study, total ginsenosides were effective against right ventricular hypertrophy, promoted systolic pressure, and reduced pulmonary pressure by controlling the ERK-1/MAPK signaling pathway [98]. Hong et al. demonstrated that the consumption of PPT-rich ginseng enhances the activation of eNOS, stimulates NO formulation, and improves the thickness of the vessel walls to attenuate hypertension [99]. Previous studies have depicted that ginsenoside Rg1 inhibited Bcl-2 and caspase-3 expression during myocardial infarction via ischemia to lower myocardial cell death and decreased left ventricular hypertrophy [100]. In another study, ginsenoside CK reduced the burden of myocardial infraction by increasing the protein kinase B(Akt) and nitrogen oxide synthetase (eNOS) followed by ischemia via the Akt/PI3K pathway [101]. Although it has also been reported that ginsenoside Rg3 mitigates myocardial ischemia-reperfusion injury (MIRI) via the AKT/eNOS and Bcl-2/Bax signaling pathways [102], ginsenoside Rd reduces MIRI via the Nrf-2/HO-1 pathway [103], and ginsenoside Rb1 inhibits cardiomyocyte autophagy via the PI3K/Akt/mTOR pathway, thus controlling MIRI [104]. Recently, ref. [105] confirmed that ginsenoside Rh2 provides anti-inflammatory and antioxidant activity on MIRI via the regulation of the Nrf2/HO-1/NLRP3 signaling pathway.

3.4. Antioxidant Activities of P. ginseng in Cancer

According to growing data, ROS are implicated in multiple steps of tumorigenesis from the initiation of the tumor to metastasis [106]. Excessive amounts of ROS in the cell or the defective antioxidant defense mechanisms quicken the cellular damage and initiate carcinogenesis [107]. It has been reported that the cancer cell initiates more ROS than their counterpart [108]. ROS play a dual role in cancer. First, the overabundance of ROS instigates autophagy, apoptosis, and cell cycle arrest signals [109][110]. Second, ROS can influence the initiation, growth, and transmission of cancer via the activation of the signaling pathways which affect cell proliferation, survivability, angiogenesis, and metastasis [106]. In general, when ROS are low to moderate, they may contribute to the initiation of a tumor, and a high amount of ROS causes massive cell damage and death, typically at the early stages of tumor formation [111]. So, it may be possible to destroy cancer cells specifically by raising oxidative stress through exogenous ROS production without significantly harming normal cells [112].

3.5. Antioxidant Activities of P. ginseng in Other Diseases

ROS play a crucial role in the development of diabetes, kidney diseases, aging, etc. [113]. Mitochondrial DNA damaged by ROS is the primary cause of aging. Oxidative damage causes mitochondrial dysfunction and the translation and multiplication of mitochondrial DNA that promotes ROS production which damages mtDNA [114]. However, ginsenoside Rd consumption for one month quickens the cellular senescence to increase the antioxidant enzyme GPx and GR in mitochondria [115]. Moreover, ginsenoside Rb2 increases SOD, CAT activities, and also blood albumin which reduces oxidative stress from the skin cell [116]. According to Ramesh et al., Korean red ginseng reduces MDA levels, creatinine, AST, ALT, and urine nitrogen at higher levels Furthermore, KRG induces SOD, GPx, GST, GR, and CAT activity in the lungs and heart [117]. Additionally, *P. ginseng* derivative syringaresinol (SYR) shows antioxidant activity and stimulated

autophagy in H_2O_2-induced Hacat cells, therefore inhibiting the mRNA expression of MMP-2 and MMP-9 related to skin aging [118]. SYR may have therapeutic potential to treat diabetic cardiomyopathy by reducing oxidative stress, fibrosis, and inflammation [119].

Furthermore, Korean red ginseng prevented the blood glucose levels in STZ-induced diabetic rats [120]. In addition, it was recognized that ginsenoside Rd consumption via acute renal failure in rats increases SOD and catalase in renal tissue and serum [121]. Recent studies have shown that ginseng triggers pro-inflammatory cytokine (IL-6, IL-1β, and TNF-α) expression as well as activates ROS-mediated pathways to show antifatigue activity through anti-oxidation and anti-inflammatory activity [122]. Research has shown that *P. ginseng* plays as anti-inflammatory, immunostimulatory, neuroprotective, hepatoprotective, antiplatelet, antidiabetic, and anti-angiogenesis roles. Korean ginseng and its ginsenosides are effective in various anti-inflammatory diseases including colitis, gastritis, and hepatitis. Han et al. depicted that ginseng shows anti-inflammatory activity by preventing Akt [123]. Moreover, Rg1 could be a useful approach for preventing acute liver damage by stimulating the Nrf2 signaling pathway [124]. Additionally, ginseng can regulate streptozotocin-induced diabetes by increasing antioxidant enzymes [125]. Moreover, ref. [126] depicted that fermented black ginseng *(P. ginseng)* can reduce ROS levels in H_2O_2-induced Hacat cells via its antioxidant activity compared to black and white ginseng. Furthermore, FBG shows higher anti-wrinkle and anti-melanogenic activity than BG and WG [127].

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